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3,824,267

**THIOLESTERS OF GUANIDINO ORGANIC ACIDS**  
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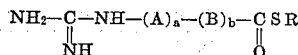
Int. Cl. C07c 129/00

U.S. Cl. 260—455 R

6 Claims

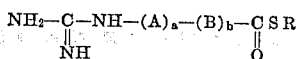
## ABSTRACT OF THE DISCLOSURE

A compound having the general formula



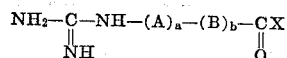
in which A is a straight chain or branched alkylene group having 1 to 10 carbon atoms, B is a bivalent aliphatic or alicyclic group,  $a$  is 0 or 1,  $b$  is 0 or 1,  $a+b$  is 1 or 2 and R is any one of the straight chain or branched alkyl group and carbethoxyalkyl group having 1 to 10 carbon atoms, alicyclic group, aromatic group and phenylalkyl group, each of the above-mentioned alicyclic group and aromatic group may be substituted by a lower alkyl group, carbethoxy group, carbethoxy lower alkyl group, carboxy lower alkyl group, halogen, alkoxy group, acylamide group, alkylsulfonyl group, carboxy group, thiocarboxy group, mercaptocarbonyl group, nitro group or carbonyl group.

This invention relates to thiolesters of guanidinoorganic acids of the general formula:



wherein A is a straight chain or branched alkylene group having 1 to 10 carbon atoms,  $a$  is 0 or 1, B is any one of p-phenylene group, p-benzylene group and bivalent alicyclic group,  $b$  is 0 or 1,  $a+b$  is 1 or 2 and R is any one of straight chain or branched alkyl group and carbethoxyalkyl group having 1 to 10 carbon atoms, alicyclic group, aromatic group and aralkyl group and each of the above mentioned alicyclic group and aromatic group may be substituted by a lower alkyl group, carbethoxy group, carbethoxy lower alkyl group, carboxyalkyl group, halogen, alkoxy group, acrylamide group, alkylsulfonyl group, carboxy group, thiocarboxy group, mercaptocarbonyl group, nitro group or carbamoxyl group.

The present invention also relates to the production of the above mentioned thiolesters of guanidinoorganic acids and their salts with acids characterized by the reaction of guanidinoorganic acyl halides of the general formula:



(wherein A,  $a$ , B and  $b$  are as defined above, and X is halogen) with thiols of the general formula:



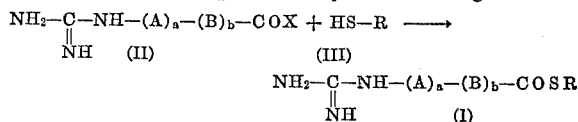
(wherein R is as defined above).

We have found that the above mentioned compounds (I) of this invention have strong antiviral action and antitrypsin action.

The above mentioned thiolesters (I) can be produced by the reaction of a guanidinoorganic acyl halide with a thiol in the presence of a dehydrohalogenation agent.

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This reaction is represented by the following formula:

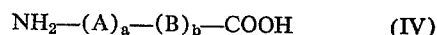


(wherein A,  $a$ , B,  $b$ , X and R are as defined above.

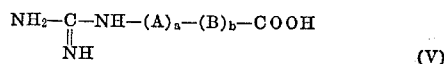
This reaction may be carried out as follows:

Thus the starting compound (III) is dissolved in a solvent and is made to react by the addition of the other compound (II) in the presence of a dehydrohalogenation agent.

The starting compounds (II) may be obtained according to the following process. That is to say, amino acids of the general formula:



are converted to guanidino acids of the general formula:



for example, by the reaction with cyanamide described in Chemische Berichte, vol. 43, page 2882 or by the reaction with S-methyl isothiurea as described in Japanese Patent Publication No. 20564/1963 or by the reaction with S-methyl nitroisothiurea, followed by the reduction of formed nitroguanidino acid. The obtained guanidino acids or their salts with organic acids, such as p-toluenesulfonic acid or methanesulfonic acid, hydrohalogenic acid, etc. are halogenized by a halogenizing reagent, such as thionyl chloride, phosphorus pentachloride, phosphorus trichloride, phosphorus pentabromide or phosphorus oxychloride, in the absence or presence of non-polar solvent, such as benzene, chloroform or carbon tetrachloride.

The reaction of the present invention will be explained in more detail. As this reaction is the condensation accompanied by the formation of hydrogen halide, it is advantageous to use a dehydrohalogenation agent to promote the reaction. As for the dehydrohalogenation agent, there can be used a tertiary amine or, if required, an inorganic base. As a tertiary organic amine, there can be used an aliphatic aromatic or heterocyclic amine, for example, triethylamine, tributylamine, dimethylaniline or pyridine. Particularly pyridine is preferable because it is useful also as a solvent. Further, as an inorganic base there can be used, for example, sodium bicarbonate, sodium carbonate or sodium hydroxide.

As a solvent there can be used, for example, benzene, toluene, tetrahydrofuran or pyridine. As described above, pyridine acts also as a dehydrohalogenation agent and is therefore particularly preferable.

Since the reaction proceeds comparatively fast, it may be carried out at the ordinary temperature or, if necessary, with a little cooling. Generally the reaction may be carried out at a temperature from 4° C. to the ordinary or room temperature.

The reaction time varies depending upon the reaction temperature to be used but it is generally 30 minutes to 4 hours, preferably 1.5 to 2.5 hours.

In carrying out the reaction, the starting material (III) is dissolved in a solvent, for example, tetrahydrofuran and the solution is added into the compound (II), and then a dehydrohalogenation agent is added thereto with stirring. Alternatively, the above compound (III) is dissolved in a solvent, preferably pyridine and the compound (II) is added to the above solution. When pyridine is used as a solvent, the compound (II) is not dissolved therein and therefore the reaction mixture is heterogeneous. However, the product (I) is soluble in pyridine, and therefore the reaction mixture becomes homogeneous with the progress of the reaction. In the case where any other sol-